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Alteplase for Acute Ischemic Stroke at 4.5 to 24 Hours
The HOPE Randomized Clinical Trial

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IMPORTANCE The safety and efficacy of intravenous thrombolytics beyond 4.5 hours after ischemic stroke onset remain inadequately studied.

OBJECTIVE To evaluate the safety and efficacy of intravenous alteplase administered 4.5 to 24 hours after stroke onset in patients with salvageable brain tissue, regardless of the presence of large vessel occlusion.

DESIGN, SETTING, AND PARTICIPANTS This randomized, open-label, blinded end-point trial was conducted at 26 stroke centers across China. A total of 372 patients with acute ischemic stroke and salvageable brain tissue identified by perfusion imaging were enrolled between June 21, 2021, and June 30, 2024 (final follow-up October 2, 2024). Eligibility criteria included stroke onset (or the midpoint between last known well and symptom recognition if onset was unknown) of 4.5 to 24 hours prior to presentation, and no initial plan for endovascular thrombectomy. Data were analyzed from December 2024 to February 2025.

INTERVENTIONS Patients were randomly assigned (1:1) using a minimization algorithm to receive intravenous alteplase (0.9 mg/kg; maximum dose, 90 mg; n = 186) or standard medical treatment (n = 186).

MAIN OUTCOMES AND MEASURES The primary efficacy outcome was functional independence, defined as a modified Rankin Scale score of 0 to 1 at 90 days. Safety outcomes included symptomatic intracranial hemorrhage within 36 hours and all-cause mortality within 90 days.

RESULTS Among 372 patients who were enrolled (median [IQR] age, 72 [64-80] years; 160 [43%] women), all completed the trial. The primary outcome occurred in 75 of 186 patients (40%) in the alteplase group and 49 of 186 (26%) in the control group (adjusted risk ratio, 1.52 [95% CI, 1.14-2.02]; *P* = .004; unadjusted risk difference, 13.98% [95% CI, 4.50%-23.45%]). The incidence of symptomatic intracranial hemorrhage was higher with alteplase at 3.8% compared with 0.51% with standard treatment (adjusted risk ratio, 7.34 [95% CI, 1.54-34.84]; *P* = .01; unadjusted risk difference, 3.23% [0.28%-6.19%]), and mortality was 11% in both groups (adjusted risk ratio, 0.91 [95% CI, 0.52-1.62]; *P* = .76; unadjusted risk difference, 0% [95% CI, −6.30% to 6.30%]).

CONCLUSIONS AND RELEVANCE In patients with acute ischemic stroke with salvageable brain tissue identified by perfusion imaging who did not initially receive thrombectomy, intravenous alteplase administered 4.5 to 24 hours after onset provided functional benefit, despite an increase in symptomatic intracranial hemorrhage.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT04879615

Visual Abstract

Supplemental content

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Group Information: A full list of the HOPE Investigators appears in Supplement 4.

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Over recent decades, intravenous thrombolysis (IVT) has been the cornerstone of ischemic stroke reperfusion therapy.[1,2] The standard therapeutic window of treatment within 4.5 hours of symptom onset involves use of clinical and noncontrast computed tomographic (CT) criteria to identify patients who are candidates for IVT.[1,2] The previous expansion in time from 3 to 4.5 hours after onset[3] increased the pool of potentially eligible patients by 30%.[4] However, the majority of patients with stroke present beyond 4.5 hours, and further extension of the treatment window to within 24 hours of symptom onset could substantially increase eligibility if patients are selected appropriately.[4]

Advances in perfusion imaging and standardized postprocessing techniques have refined patient selection by facilitating the identification of salvageable brain tissue on imaging studies. The EXTEND trial and subsequent meta-analysis demonstrated significant net benefits of IVT with alteplase in patients presenting within 4.5 to 9 hours of stroke onset (or the midpoint of sleep for wake-up stroke) who had a perfusion mismatch profile identified on imaging studies.[5,6] Evidence suggests that in patients with robust collateral circulation, salvageable ischemic tissue may persist beyond 24 hours, highlighting the potential to extend the therapeutic window even further.[7,8] More recently, the TIMELESS and TRACE-3 trials evaluated IVT with tenecteplase in patients with large vessel occlusion treated within 4.5 to 24 hours of symptom onset, confirming safety but yielding inconsistent efficacy outcomes.[9,10] Notably, in TIMELESS,[9] a large proportion of patients underwent rapid thrombectomy, which may have influenced the observed effect of thrombolysis. Patients with distal vessel occlusions were not included in these trials, although they may also potentially benefit from IVT in an extended time window.[11]

Thrombectomy is often unavailable in low- and middle-income countries. The Treatment With Intravenous Alteplase in Ischemic Stroke Patients With Onset Time Between 4.5 and 24 Hours (HOPE) trial was designed to evaluate whether patients with potentially salvageable brain tissue, for whom thrombectomy was not initially planned, could benefit from IVT within an extended treatment window of 4.5 to 24 hours after symptom onset. Given the widespread availability of CT imaging across diverse stroke centers, CT perfusion was used to estimate the irreversibly injured ischemic core and potentially salvageable penumbra. Notably, the presence or absence of large vessel occlusion was not a criterion for patient inclusion in this trial.

Key Points

Question Does intravenous alteplase administered 4.5 to 24 hours after acute ischemic stroke onset improve outcomes in patients with salvageable brain tissue and no initial plan for thrombectomy?

Findings In this randomized clinical trial of 372 patients, 40% receiving alteplase achieved functional independence at 90 days vs 26% with standard care, a statistically significant difference.

Meaning In patients with salvageable brain tissue identified by perfusion imaging who did not initially receive thrombectomy, alteplase given 4.5 to 24 hours after acute ischemic stroke onset may improve functional outcomes.

Methods

Study Design

We conducted a randomized, open-label, blinded end-point trial at 26 stroke centers in China (eAppendix 1 and eFigure 1 in Supplement 1).[12] The list of centers, investigators, and committee members is available in eAppendix 2 in Supplement 1. The protocol and statistical analysis plan are available in Supplement 2 and Supplement 3. The steering committee oversaw the trial design, execution, and analysis, with safety monitored by an independent data and safety monitoring board. The trial protocol was approved by the institutional review boards of the Second Affiliated Hospital of Zhejiang University, School of Medicine, and each participating site. Written informed consent was obtained from all patients or their legally authorized representatives prior to enrollment. The trial was conducted in accordance with the Declaration of Helsinki[13] and International Council for Harmonization guidelines for Good Clinical Practice. This article adheres to the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Participants

Patients with ischemic stroke and potentially salvageable tissue on CT perfusion imaging presenting 4.5 to 24 hours after stroke onset (for stroke on waking or unwitnessed stroke, the midpoint of the time last known to be well and symptom recognition time was used) were recruited. More specifically, eligible patients were 18 years or older and had clinical signs of stroke that began within 4.5 to 24 hours of presentation; a score of 4 to 26 on the National Institutes of Health Stroke Scale (NIHSS) (range, 0-42; higher scores indicate greater severity of neurological deficits); a prestroke score of 0 or 1 on the modified Rankin Scale (mRS) (range, 0-6; higher scores indicate increasing levels of disability); and potentially salvageable tissue on CT perfusion imaging (ischemic core volume ≤70 mL, a ratio of the volume of hypoperfused tissue to the ischemic core volume of at least 1.2, and a difference in volume between the hypoperfused tissue and the ischemic core of at least 10 mL), where the ischemic core was estimated as the area with a cerebral blood flow of less than 30% of that in normal brain and the hypoperfused region was defined according to a delayed arrival of an injected tracer agent (time to maximum of the residue function of >6 seconds).

For patients with large vessel occlusion and guideline eligibility for thrombectomy, the decision regarding thrombectomy was made prior to potential enrollment in this trial. Patients and families were fully informed about the potential benefits and risks of thrombectomy, and only those who explicitly declined the procedure were evaluated for trial participation. The discussion and decision regarding thrombectomy were conducted independently from trial enrollment to

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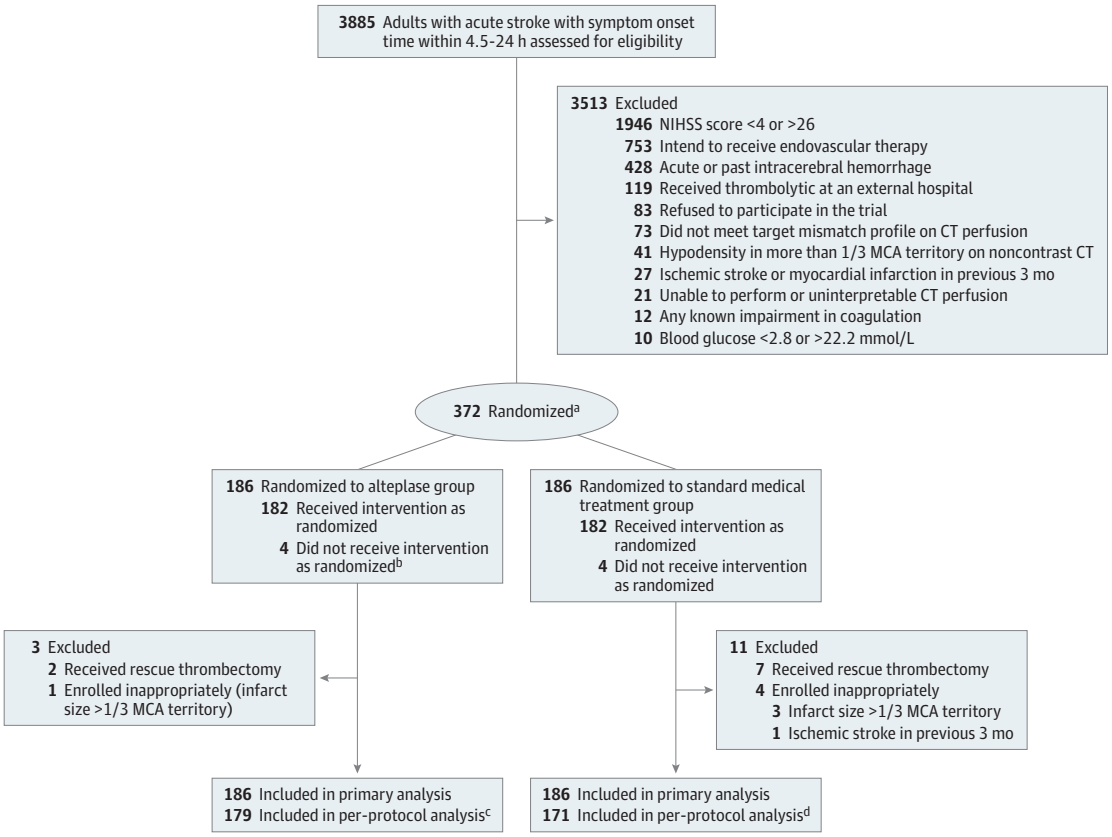
Figure 1. Flow of Patient Recruitment, Randomization, and Follow-Up in the HOPE Trial


3885 Adults with acute stroke with symptom onset time within 4.5-24 h assessed for eligibility
3513 Excluded
1946 NIHSS score <4 or >26
753 Intend to receive endovascular therapy
428 Acute or past intracerebral hemorrhage
119 Received thrombolytic at an external hospital
83 Refused to participate in the trial
73 Did not meet target mismatch profile on CT perfusion
41 Hypodensity in more than 1/3 MCA territory on noncontrast CT
27 Ischemic stroke or myocardial infarction in previous 3 mo
21 Unable to perform or uninterpretable CT perfusion
12 Any known impairment in coagulation
10 Blood glucose <2.8 or >22.2 mmol/L
372 Randomized[a]
186 Randomized to alteplase group
182 Received intervention as randomized
4 Did not receive intervention as randomized[b]
186 Randomized to standard medical treatment group
182 Received intervention as randomized
4 Did not receive intervention as randomized
3 Excluded
2 Received rescue thrombectomy
1 Enrolled inappropriately (infarct size >1/3 MCA territory)
11 Excluded
7 Received rescue thrombectomy
4 Enrolled inappropriately
3 Infarct size >1/3 MCA territory
1 Ischemic stroke in previous 3 mo
186 Included in primary analysis
179 Included in per-protocol analysis[c]
186 Included in primary analysis
171 Included in per-protocol analysis[d]

CT indicates computed tomography. To convert glucose to mg/dL, multiply mmol/L values by 0.0555.

[a]Randomization was conducted using a centralized, web-based system employing a stochastic minimization algorithm, with stratification based on age (<70 or ≥70 years), time from symptom onset to randomization (<9 or ≥9 hours), and National Institutes of Health Stroke Scale (NIHSS) score at randomization (<10 or ≥10).

[b]One patient crossed over to the standard treatment group and received rescue thrombectomy.

[c]Seven patients were excluded due to protocol violations, including 4 who crossed over to the standard treatment group, 1 with infarct size >1/3 middle cerebral artery (MCA) territory, and 2 who received rescue thrombectomy.

[d]Fifteen patients were excluded due to protocol violations, including 4 who crossed over to the alteplase group, 3 with infarct size >1/3 MCA territory, 1 with a history of ischemic stroke in the previous 3 months, and 7 who received rescue thrombectomy.

ensure that participation in the study did not influence clinical care decisions.

Patients were excluded if thrombectomy was planned at the time of randomization or if they had guideline-based contraindications to alteplase, aside from the extended time window. The detailed inclusion and exclusion criteria have been published previously and are listed in the eMethods in Supplement 1.[14]

Randomization and Masking

Eligible participants were randomly assigned (1:1) to either the alteplase group or the standard treatment group using a centralized, secure, web-based system (**Figure 1**). A stochastic minimization algorithm was used to balance the groups based on age (<70 or ≥70 years), time from symptom onset to randomization (<9 or ≥9 hours), and NIHSS score at randomization (<10 or ≥10), while maintaining randomization concealment through incorporation of randomness to prevent predictability of treatment assignment. The local investigators accessed the web-randomization system to complete the treatment assignment. Treatment assignment was open label. However, evaluators conducting clinical assessments and the independent adjudication committee, responsible for reviewing primary and secondary efficacy outcomes as well as bleeding events, remained blinded to the treatment group assignments.

Intervention and Other Procedures

The alteplase group received intravenous alteplase at 0.9 mg/kg (maximum 90 mg), with 10% administered as a bolus over 1 minute followed by a 60-minute infusion of the remaining dose. After 24 hours, patients in this group received standard poststroke care, including antiplatelet therapy if indicated, consistent with established clinical principles and medical practice guidelines. The standard treatment group received antiplatelet therapy and other supportive care based on the same guidelines from the time of randomization.

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Patients initially planned to undergo endovascular thrombectomy during screening were excluded, but rescue thrombectomy was permitted after randomization. At screening, demographic data, medical history, medications, laboratory test results, neurological function (mRS and NIHSS scores), and imaging were collected. Baseline CT perfusion imaging confirmed eligibility and hemorrhagic transformation was assessed by CT or magnetic resonance imaging (MRI) between 24 and 36 hours after randomization.

Outcomes

The primary outcome was the percentage of patients achieving nondisabled functional outcome, defined as mRS score of 0 to 1 at 90 days. The assessments were performed by certified personnel who were blinded to treatment assignments. For patients followed up by telephone, audio recordings were reviewed centrally by trained raters. In cases in which audio recordings were unavailable, the mRS score was assessed in person by local certified investigators who were also blinded to group assignment.

Secondary outcomes included the percentage of patients achieving independent recovery, defined as mRS score of 0 to 2 at 90 days; the proportion of patients achieving mRS score of 0 to 3 at 90 days; the ordinal distribution of mRS scores at 90 days; and major neurologic improvement defined as an improvement of at least 8 points on the NIHSS compared with the initial deficit or a score of less than 1 achieved at 24 hours and 7 days.

Safety outcomes included symptomatic intracranial hemorrhage (defined as any intracranial hemorrhage judged to be the primary cause of neurologic deterioration causing a ≥4-point worsening in NIHSS score or death) within 36 hours after randomization,[3] parenchymal hematoma within 36 hours,[15] and all-cause mortality within 90 days. Adverse events were recorded using the National Cancer Institute's *Common Terminology Criteria for Adverse Events, Version 5.0*.

Sample Size Calculation

The sample size was estimated based on data from a previous observational cohort at the coordinating center, which included 62 patients (34 in the IVT group and 28 in the standard therapy group) presenting with clinical signs of stroke within 4.5 to 24 hours of symptom onset using the same eligibility criteria as the HOPE trial. In this cohort, the percentage of patients achieving an mRS score of 0 to 1 at 90 days was 35% in the intervention group and 21% in the control group. Based on these estimates and assuming a 15% dropout rate, a sample size of 372 patients (186 per group) was calculated to provide 80% power to detect a significant treatment effect (an absolute difference of 14%) with a 2-sided type I error rate of .05.

Statistical Analysis

The primary analysis included all randomized patients with available mRS scores at 90 days, including those who died during follow-up (assigned an mRS score of 6), analyzed according to the group to which they were randomized. The safety analysis included all randomized patients who completed at least 1 safety outcome assessment. Patients who were found not to meet the inclusion criteria after randomization, as well as those who underwent rescue thrombectomy after randomization, were excluded from the per-protocol analysis but remained in the primary analysis set to preserve the benefits of randomization.

We prespecified covariate-adjusted modified Poisson regression with robust standard error estimation[16] to compare the 2 treatment groups for the primary outcome analysis, as well as for the analyses of dichotomous secondary efficacy and safety outcomes. All analyses were adjusted for age, NIHSS score at randomization, and time from onset to randomization, and results are presented as adjusted risk ratios with 95% CIs. An earlier version of the protocol had specified logistic regression analysis to generate odds ratios,[14] and these analyses are reported as sensitivity analyses. The treatment effect across the full range of mRS scores was assessed using an ordinal logistic regression (proportional odds) model, with results expressed as a common odds ratio for improvement toward better functional outcomes. The model was adjusted for age, NIHSS score at randomization, and time from symptom onset to randomization. The protocol prespecified merging of mRS score categories 5 and 6 to avoid counting a shift from death to severe disability as a treatment success in the ordinal analysis. The data for the main efficacy analyses were complete; therefore, no imputation for missing data was needed. As an additional sensitivity analysis, we excluded the patients whose centrally reprocessed perfusion imaging results did not meet the protocol-defined thresholds, although they were retained in the per-protocol population.

Prespecified subgroups were categorized based on age (<80 vs ≥80 years), sex, initial NIHSS score at randomization (<10 vs ≥10), category of onset of stroke (4.5-9 hours vs 9-24 hours vs unknown stroke onset time), presence of vessel occlusion (internal carotid artery vs M1 segment of middle cerebral artery vs M2 segment of middle cerebral artery vs other arteries), and stroke classification. In addition to the prespecified analyses, we conducted 2 main post hoc analyses. First, to evaluate the impact of perfusion mismatch eligibility criteria from prior trials on the primary outcome, we compared patients who met or did not meet the EXTEND and TRACE-3 trial criteria.[4,9] Second, given the relatively large enrollment from the coordinating center, a post hoc subgroup analysis was performed comparing the primary outcome between patients enrolled at the coordinating center and those from other participating sites in both the primary analysis set and per-protocol populations.

No interim analysis was planned for this trial. However, an independent data and safety monitoring committee regularly reviewed safety data to determine whether the study should proceed. A 2-sided *P* value of less than .05 was considered to indicate statistical significance. Given the lack of adjustment for multiplicity, the analyses of secondary end points should be interpreted as exploratory in nature. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute). The full statistical analysis plan is provided in Supplement 3.

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Results

Patient Characteristics

Between June 21, 2021, and June 30, 2024, a total of 372 patients were enrolled in the trial; 186 were randomized to receive intravenous alteplase and 186 to receive standard medical treatment. The enrolled patients were generally representative of the expected study population (eTable 1 in Supplement 1). Eligibility for thrombectomy among patients with large vessel occlusion and reasons for not receiving thrombectomy are summarized in eTable 2 in Supplement 1. Figure 1 provides details regarding protocol violations that occurred during the trial. Four patients in the control group crossed over to receive alteplase and 4 patients in the alteplase group crossed over to receive standard medical treatment. Rescue thrombectomy was performed in 3 patients in the alteplase group (including one who also crossed over) and 7 in the standard medical treatment group. Of these patients, 8 initially declined thrombectomy despite being eligible, but later deteriorated neurologically and received treatment after reconsent. Two patients had mild symptoms at randomization and were not initially eligible; thrombectomy was performed after clinical worsening and reassessment.

The demographic and clinical characteristics of the patients were similar in the 2 groups at baseline (**Table 1**). The median (IQR) age was 72 (64-80) years and 160 patients (43.0%) were female. The median (IQR) NIHSS score at randomization was 10 (6-15). Overall, 13.7% of the patients (n = 51) received the assigned intervention in the later time window (>9 to 24 hours after stroke onset) and 34.7% (n = 129) in the earlier time window (>4.5 to 9 hours after stroke onset); the remainder (51.6% [n = 192]) discovered stroke symptoms on awakening or had unwitnessed onset. Distal occlusions beyond the internal carotid artery, M1 or proximal M2 segment of the middle cerebral artery, or vertebral or basilar artery were observed in 136 of 372 patients (36.6%), involving distal middle cerebral artery branches (n = 96), anterior cerebral artery (n = 21), and posterior cerebral artery (n = 9), with no definite occlusion identified in 10 patients.

Primary Outcome

The primary outcome of nondisabled functional outcome (defined as a mRS score of 0 or 1) at 90 days occurred in 40.3% in the alteplase group compared with 26.3% in the standard-treatment group (75 vs 49 patients; adjusted risk ratio, 1.52 [95% CI, 1.14-2.02]; P = .004), with an unadjusted absolute risk difference of 13.98% (95% CI, 4.50%-23.45%) (**Table 2** and **Figure 2**); similar results were observed in the per-protocol analysis (Figure 2; eTable 3 in Supplement 1). The primary outcome was assessed by blinded central raters using audio recordings in 352 patients (94.6%), by local blinded investigators in 8 patients (2.1%), and based on known fatal outcomes in 12 patients (3.2%).

Secondary Outcomes

Secondary outcomes are also presented in Table 2. The median (IQR) mRS score was 2 (1-4) in the alteplase group and 3 (1-4) in the standard medical treatment group. The common

Table 1. Baseline Characteristics in the Full Analysis Set

	Alteplase (n = 186)	Standard medical treatment (n = 186)
Age, median (IQR), y	72 (62-80)	73 (65-80)
<70, No. (%)	78 (41.9)	73 (39.2)
≥70, No. (%)	108 (58.1)	113 (60.8)
Sex, No. (%)[a]		
Male	102 (54.8)	110 (59.1)
Female	84 (45.2)	76 (40.9)
Medical history, No. (%)[b]		
Hypertension	131 (70.4)	135 (72.6)
Diabetes	50 (26.9)	48 (25.8)
Atrial fibrillation	36 (19.4)	45 (24.2)
Previous ischemic stroke	33 (17.7)	29 (15.6)
Dyslipidemia	18 (9.7)	20 (10.8)
Coronary heart disease	13 (7.0)	16 (8.6)
Current smoking	56 (30.1)	57 (30.6)
Prior medication use, No. (%)		
Antiplatelet agents	19 (10.2)	21 (11.3)
Anticoagulant agents	3 (1.6)	3 (1.6)
mRS score before stroke, No. (%)[c]		
0	177 (95.2)	172 (92.5)
1	9 (4.8)	14 (7.5)
NIHSS score at randomization, median (IQR)[d]	10 (6-15)	10 (6-14)
<10, No. (%)	91 (48.9)	89 (47.8)
≥10, No. (%)	95 (51.1)	97 (52.2)
Onset to imaging time, median (IQR), min	398 (315-537)	414 (334-528)
Onset to randomization time, median (IQR), min	411 (328-551)	427 (352-542)
<540 min, No. (%)	138 (74.2)	139 (74.7)
≥540 min, No. (%)	48 (25.8)	47 (25.3)
Door-to-needle time, median (IQR), min	66 (49-93)	
Category of onset of stroke, No. (%)		
Known onset time	88 (47.3)	92 (49.5)
Stroke on awakening	76 (40.9)	73 (39.2)
Unwitnessed onset	22 (11.8)	21 (11.3)
Baseline ASPECTS, median (IQR)[e]	9 (8-10)	9 (8-10)
Ischemic core at initial imaging, median (IQR), ml[f]	12 (4-28)	14 (4-28)
Perfusion lesion at initial imaging, median (IQR), ml[g]	49 (29-85)	52 (30-81)

(continued)

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Table 1. Baseline Characteristics in the Full Analysis Set (continued)

	Alteplase (n = 186)	Standard medical treatment (n = 186)
Vessel occlusion, No. (%)[h]		
Internal carotid artery	33 (17.7)	39 (21.0)
M1 segment of middle cerebral artery	51 (27.4)	46 (24.7)
Proximal M2 segment of middle cerebral artery	21 (11.3)	26 (14.0)
Distal M2 segment of middle cerebral artery	15 (8.1)	18 (9.7)
Distal middle cerebral artery beyond M2	38 (20.4)	25 (13.4)
Anterior cerebral artery	9 (4.8)	12 (6.5)
Posterior cerebral artery	4 (2.2)	5 (2.7)
Basilar artery	9 (4.8)	8 (4.3)
Vertebral artery	2 (1.1)	1 (0.5)
No definite occlusion	4 (2.2)	6 (3.2)
Endovascular treatment, No. (%)	3 (1.6)	7 (3.8)

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; CT, computed tomographic; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

[a] Sex as reported by the patient and confirmed by official identification.

[b] Comorbidities obtained from patient or family report.

[c] The mRS scores (0-6) reflect increasing levels of disability, with 0 indicating no symptoms and 6 indicating death. The pre-stroke mRS score was determined by inquiring with the patient or their legal representative about the patient's ability to perform activities of daily living prior to hospitalization for the stroke.

[d] The NIHSS scores range from 0 to 42, with higher scores indicating greater severity of neurological deficits.

[e] The ASPECTS ranges from 0 to 10, with higher scores indicating less extensive ischemic injury. For 34 patients with posterior circulation (PC) stroke, the PC-ASPECTS was used, which has a similar scoring range and interpretation. Values reflect central imaging core laboratory assessment.

[f] The ischemic core was identified as regions with a relative cerebral blood flow of less than 30% compared to normal brain tissue, as assessed by CT perfusion imaging.

[g] Critically hypoperfused tissue was defined as the perfusion lesion volume, representing the area where the arrival time of an injected tracer agent was delayed by more than 6 seconds.

[h] Vessel occlusion was determined based on either a dedicated CT angiography or reconstructed from the arterial phase of CT perfusion.

odds ratio for the ordinal distribution of scores on the mRS at 90 days (merging scores of 5 and 6) was 1.51 (95% CI, 1.04-2.18; P = .03), indicating greater odds of a better functional outcome among the alteplase group (Table 2). In the per-protocol analysis, the common odds ratio was 1.41 (95% CI, 0.96-2.06; P = .08), and the results for other secondary outcomes were similar to those of the primary analyses (eTable 3 in Supplement 1).

Subgroup, Sensitivity, and Post Hoc Analyses

The effect of alteplase on the primary outcome in prespecified subgroups is shown in **Figure 3** for the primary analysis and in eFigure 2 in Supplement 1 for the per-protocol analysis. The results were generally consistent across subgroups, except for stroke classification, in which a significant interaction was observed (interaction P = .02 in the primary analysis and interaction P = .03 in the per-protocol analysis). The results of sensitivity analyses of functional outcomes, adjusted for age, NIHSS score at randomization, and time from symptom onset to randomization, using logistic regression to generate odds ratios, are presented in the eTable 4 in Supplement 1. In a post hoc sensitivity analysis excluding 9 patients whose centrally reprocessed perfusion imaging did not meet the predefined thresholds, the results remained consistent with the primary findings (adjusted risk ratio, 1.46 [95% CI, 1.08-1.97]; P = .01), as shown in eTable 5 in Supplement 1. The HOPE trial used the perfusion mismatch imaging criteria of EXTEND,[4] with 260 enrolled patients (69.9%) meeting the perfusion mismatch criteria of TRACE-3.[9] The results of a post hoc analysis comparing the primary outcome in patients who did or did not meet EXTEND and TRACE-3 eligibility criteria[4,9] are presented in the eTable 6 in Supplement 1. A post hoc subgroup analysis comparing patients enrolled at the coordinating center vs other sites showed no significant difference in the effect of alteplase on the primary outcome in the primary (interaction P = .59) and per-protocol (interaction P = .36) analyses, respectively (eTable 7 in Supplement 1).

Adverse Events

Symptomatic intracranial hemorrhage within 36 hours after randomization occurred in 7 patients (3.8%) in the alteplase group and in 1 (0.5%) in the standard medical treatment group (adjusted risk ratio, 7.34 [95% CI, 1.54-34.84]; P = .01) (Table 2). Parenchymal hematoma was reported in 14 patients (7.6%) in the alteplase group and in 6 patients (3.3%) in the standard treatment group (adjusted risk ratio, 2.14 [95% CI, 0.87-5.26]; P = .10) (Table 2). The percentage of patients who died within 90 days after randomization was 10.8% (20 of 186 patients) in the alteplase group and 10.8% (20 of 186 patients) in the standard treatment group (adjusted risk ratio, 0.91 [95% CI, 0.52-1.62]; P = .76) (Table 2). The incidence of adverse events and serious adverse events by system organ class are presented in eTable 8 and eTable 9 in Supplement 1.

Discussion

This trial showed that, in patients with stroke who had salvageable brain tissue and for whom endovascular thrombectomy was not initially planned, treatment with intravenous alteplase between 4.5 and 24 hours after stroke onset resulted in a higher percentage of patients achieving a nondisabled functional outcome based on mRS scores compared with standard medical treatment. Secondary outcomes of functional independence, ordinal analysis of mRS, and early neurological recovery provided supportive evidence for the benefit of alteplase. The incidence of symptomatic intracranial hemorrhage within the first 36 hours after randomization was higher

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Table 2. Trial Outcomes in the Full Analysis Set and Safety Population

	Alteplase (n = 186)	Standard medical treatment (n = 186)	Unadjusted risk difference, % (95% CI)	Effect size (95% CI)[a]	*P* value
Primary outcome					
mRS score 0-1 at 90 d, No. (%)[b]	75 (40.3)	49 (26.3)	13.98 (4.50 to 23.45)	1.52 (1.14 to 2.02)	.004
Secondary outcomes					
Distribution of mRS score at 90 d [merging 5-6], median (IQR)	2 (1-4)	3 (1-4)		1.51 (1.04 to 2.18)	.03
0	41 (22.0)	25 (13.4)			
1	34 (18.3)	24 (12.9)			
2	28 (15.1)	36 (19.4)			
3	17 (9.1)	29 (15.6)			
4	27 (14.5)	28 (15.1)			
5	19 (10.2)	24 (12.9)			
6	20 (10.8)	20 (10.8)			
mRS score 0-2 at 90 d, No. (%)	103 (55.4)	85 (45.7)	9.68 (−0.44 to 19.79)	1.20 (1.00 to 1.45)	.052
mRS score 0-3 at 90 d, No. (%)	120 (64.5)	114 (61.3)	3.23 (−6.59 to 13.04)	1.05 (0.91 to 1.22)	.47
Major neurologic improvement at 24 h, No. (%)[c]	39 (21.0)	24 (12.9)	8.06 (0.49 to 15.64)	1.66 (1.03 to 2.66)	.04
Major neurologic improvement at 7 d, No. (%)[c]	65/183 (35.5)	50/184 (27.2)	8.35 (−1.11 to 17.80)	1.30 (0.95 to 1.77)	.10
Safety outcomes					
Death within 90 d, No. (%)	20 (10.8)	20 (10.8)	0.0 (−6.30 to 6.30)	0.91 (0.52 to 1.62)	.76
Symptomatic intracranial hemorrhage within 36 h, No. (%)[d]	7/185 (3.8)	1/182 (0.5)	3.23 (0.28 to 6.19)	7.34 (1.54 to 34.84)	.01
Parenchymal hematoma within 36 h, No. (%)[e]	14/185 (7.6)	6/182 (3.3)	4.27 (−0.34 to 8.88)	2.14 (0.87 to 5.26)	.10

Abbreviations: mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale.

[a] Treatment effects are presented as adjusted risk ratios with 95% confidence intervals for all outcomes, except for the ordinal distribution of scores on the mRS, which is reported as an adjusted common odds ratio (with data combined for scores of 5 and 6). Adjustments were made for age, NIHSS score at randomization, and time from onset to randomization.

[b] The mRS scores (0-6) reflect increasing levels of disability, with 0 indicating no symptoms and 6 indicating death.

[c] Major neurologic improvement was defined as a reduction of at least 8 points from the baseline NIHSS score or achieving an NIHSS score of 1 or lower. The NIHSS scores range from 0 to 42, with higher scores indicating greater severity of neurological deficits.

[d] Symptomatic intracranial hemorrhage was defined as any hemorrhage that was associated with clinical deterioration, reflected by a worsening of neurological status by 4 or more points on the NIHSS compared to baseline, or that leads to death and is identified as the predominant cause of neurological worsening.

[e] Parenchymal hemorrhage was defined as a type of hemorrhagic transformation characterized by a blood clot within the infarcted brain tissue, occupying a substantial portion of the infarct with associated mass effect.

in the alteplase group than in the standard treatment group. However, there was no difference in 90-day mortality between the 2 groups.

This trial contributes to the evidence base that supports the applicability of IVT beyond the 9-hour window established by the EXTEND trial that included patients with both large and distal medium vessel occlusions.[5] Although alteplase has been the standard thrombolytic for stroke in use for decades, recent trials have demonstrated noninferiority of tenecteplase, a genetically modified form of alteplase with longer half-life permitting bolus administration.[17-21] The TRACE-3 trial demonstrated that IV tenecteplase administered 4.5 to 24 hours post stroke improved disability-free outcomes in patients with large vessel occlusion anterior circulation stroke who lacked access to thrombectomy.[10] The authors highlighted the relevance of their findings to patients who initially presented to nonthrombectomy hospitals and required transfer because stroke progression in transit may have rendered them ineligible for thrombectomy by the time they arrived at the receiving center. Although all centers participating in the current trial had thrombectomy capabilities, these findings also have implications for settings in which access to endovascular therapy may be delayed or limited. In contrast to the current and TRACE-3 results, the TIMELESS trial, which tested the effect of tenecteplase in the 4.5- to 24-hour window among patients with salvageable tissue who did have access to endovascular therapy, did not demonstrate a benefit. This was likely due to most patients receiving thrombectomy soon (median of 15 minutes) after administration of the study drug, allowing insufficient dwell time for the thrombolytic to be effective.[9] Compared with the TRACE-3 and TIMELESS trials that also had a 24-hour window but were limited to patients with large vessel occlusions,[9,10] the current trial broadens the eligible population of patients to include those with more distal occlusions, in addition to strengthening the data for patients with large vessel occlusion. Recent trials have demonstrated that patients with distal medium vessel occlusion do not benefit from endovascular thrombectomy.[22,23] This trial indicates that alteplase may be an effective treatment option up to 24 hours after onset for patients without proximal large vessel occlusion, who constituted 37% of the trial population.

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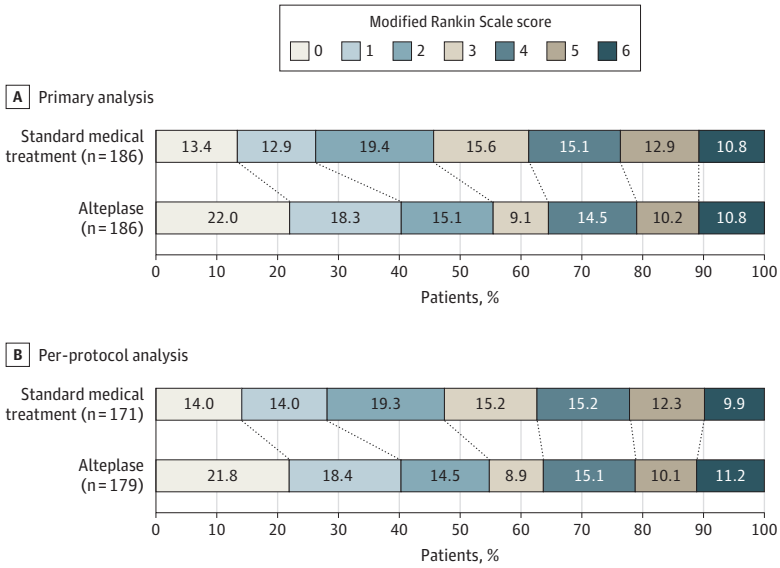
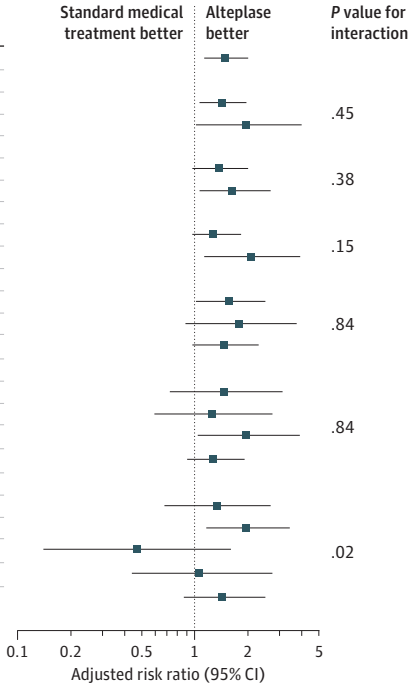
Figure 2. Distribution of Modified Rankin Scale Scores at 90 Days


Modified Rankin Scale score
0 1 2 3 4 5 6
A Primary analysis
Standard medical treatment (n = 186)
13.4 12.9 19.4 15.6 15.1 12.9 10.8
Alteplase (n = 186)
22.0 18.3 15.1 9.1 14.5 10.2 10.8
0 10 20 30 40 50 60 70 80 90 100
Patients, %
B Per-protocol analysis
Standard medical treatment (n = 171)
14.0 14.0 19.3 15.2 15.2 12.3 9.9
Alteplase (n = 179)
21.8 18.4 14.5 8.9 15.1 10.1 11.2
0 10 20 30 40 50 60 70 80 90 100
Patients, %

Scores on the modified Rankin Scale (mRS) range from 0 to 6, with higher scores indicating greater disability. A score of 0 indicates no symptoms; 1, symptomatic but nondisabled; 2, disabled but independent; 3, dependent but ambulatory; 4, not ambulatory nor capable of body self-care; 5, severe disability requiring constant care; and 6, death. Percentages may not total to 100 because of rounding.

Figure 3. Subgroup Analyses for the Primary Outcome in the Primary Analysis Population

Source	Patients with mRS score of 0 or 1 at 90 d, No./total No. (%)		Adjusted risk ratio (95% CI)
	Alteplase	Standard medical treatment	
Overall	75/186 (40.3)	49/186 (26.3)	1.52 (1.14-2.02)
Age, y			
<80	60/133 (45.1)	40/132 (30.3)	1.46 (1.07-1.98)
≥80	15/53 (28.3)	9/54 (16.7)	2.03 (1.01-4.07)
Sex			
Male	38/102 (37.3)	32/110 (29.1)	1.41 (0.98-2.02)
Female	37/84 (44.0)	17/76 (22.4)	1.69 (1.06-2.68)
NIHSS score at randomization			
<10	50/91 (54.9)	37/89 (41.6)	1.32 (0.97-1.82)
≥10	25/95 (26.3)	12/97 (12.4)	2.13 (1.14-3.96)
Category of onset of stroke			
>4.5 to 9 h	31/67 (46.3)	18/62 (29.0)	1.60 (1.02-2.51)
>9 to 24 h	7/21 (33.3)	10/30 (33.3)	1.83 (0.89-3.76)
Unknown stroke onset time	37/98 (37.8)	21/94 (22.3)	1.50 (0.97-2.32)
Occlusion site			
Internal carotid artery	8/33 (24.2)	9/39 (23.1)	1.51 (0.72-3.15)
M1 segment of middle cerebral artery	15/51 (29.4)	8/46 (17.4)	1.28 (0.59-2.77)
M2 segment of middle cerebral artery	16/36 (44.4)	10/44 (22.7)	2.03 (1.05-3.92)
Other arteries	36/66 (54.5)	22/57 (38.6)	1.32 (0.91-1.92)
Stroke classification			
Cardioembolism	11/44 (25.0)	11/55 (20.0)	1.36 (0.68-2.71)
Intracranial atherosclerosis	29/61 (47.5)	14/64 (21.9)	2.01 (1.18-3.43)
Extracranial atherosclerosis	2/23 (8.7)	7/24 (29.2)	0.48 (0.14-1.61)
Small vessel occlusion	4/9 (44.4)	6/12 (50.0)	1.10 (0.44-2.77)
Undetermined or other etiology	29/49 (59.2)	11/31 (35.5)	1.48 (0.87-2.50)



Scores on the modified Rankin Scale (mRS) range from 0 to 6, with higher scores indicating greater disability. The National Institutes of Health Stroke Scale (NIHSS) scores range from 0 to 42, with higher scores indicating greater severity of neurological deficits. Stroke classification was determined based on medical history, clinical presentation, and available imaging findings. Large artery atherosclerosis was further categorized by anatomical location as intracranial or extracranial.

This trial used the less restrictive perfusion mismatch imaging criteria pioneered by the EXTEND trial rather than those used in TRACE-3 and TIMELESS, leading to inclusion of more patients.[5,9,10] Furthermore, while the TRACE-3 and TIMELESS trials mandated the use of specific commercial software such as iStroke and RAPID.AI for CT-perfusion reconstruction, the current trial allowed greater flexibility in software selection. This approach facilitates exploration of

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real-world clinical practices, alleviates the financial burden associated with certain commercial software packages, and helps navigate the practical challenges of standardizing imaging protocols across diverse clinical centers.

There was an increased incidence of symptomatic intracranial hemorrhage in the alteplase group in this trial, although the incidence of 3.8% was similar to the other extended time window thrombolytic studies that used perfusion imaging selection (3.0% reported in TRACE-3, 3.2% in TIMELESS, and 6.2% in EXTEND).[5,9,10] Importantly, features of this trial—namely its broader imaging criteria, inclusion of distal occlusions, and flexibility in software use—enhance the relevance of the findings to resource-constrained and geographically isolated settings. In regions where access to thrombectomy is delayed or unavailable, these data support IVT as a practical and effective stand-alone strategy. By demonstrating benefit across a heterogeneous cohort using widely applicable methods, this trial may help inform stroke care across low- and middle-income health systems.

Limitations

This trial has several limitations. First, its open-label design may have contributed to crossover between groups and bias in ascertaining outcomes; however, outcome assessments were conducted by well-trained, independent evaluators who were blinded to treatment assignments and crossover was fairly limited. Second, because patients with planned thrombectomy were excluded from the trial, the findings do not apply to use of bridging thrombolysis in the extended time window before planned thrombectomy. Third, the findings may have limited applicability to populations with different stroke mechanism profiles. In particular, the greater treatment effect observed in patients with presumed intracranial atherosclerosis-related stroke may reflect specific imaging selection patterns or underlying pathophysiology, such as more robust collateral circulation or microcirculatory improvement. In addition, inclusion of patients with a broad range of stroke severity (NIHSS scores of 4-26) may affect prognosis; however, subgroup analysis showed consistent treatment effect across severity strata. As these subgroup analyses were not adjusted for multiplicity, the findings should be considered exploratory and require confirmation in future studies.

Conclusions

In this randomized clinical trial, the administration of intravenous alteplase between 4.5 and 24 hours after stroke onset in patients with imaging-confirmed salvageable brain tissue resulted in a greater proportion of patients achieving a nondisabled functional outcome compared with standard medical treatment. There was an increase in symptomatic intracranial hemorrhage, but no significant difference in mortality. These findings support extending the therapeutic window for IVT in appropriately selected patients when endovascular thrombectomy is not initially planned or indicated.

ARTICLE INFORMATION

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